REMARKS

Status of the Claims

Claims 1, 4, 6-8, 10, 27, and 29-30 are pending in the present application. Claims 1, 4 and 6 are amended. Upon entry of this amendment, claims 1, 4, 6-8, 10, 27, and 29-30 will be pending in this application. Applicants submit that these amendments add no new matter.

Claims 1, 4 and 6 have been amended to recite "Fc receptor (FcR)" to clarify the claimed Fc receptor. Support for these amendments are found throughout the application as originally filed, at least, for example, at page 2, line 25 to page 3, line 2.

Interview Summary

Applicants would like to the thank the Examiner and her supervisor for discussing this case during the telephonic interview of September 21, 2005. During the interview, while no conclusion was reached, Applicants discussed the references "Gillies," "Gray," and "Ravetch" cited *infra*, and ways that the rejection under 35 U.S.C. § 103(a) might be overcome. Applicants also discussed the rejection outlined on page 2 of the Office Action, mailed June 21, 2005, noting that claims 1, 6-8, 10, and 29-30 were drawn to non-elected subject matter. The Examiner and her supervisor agreed that amendments to the claims would not be necessary in order to bring the claims within the scope of the originally elected invention; rather, the Examiner agreed that claims 1, 6-8, 10, and 29-30 would be rejoined to the originally elected invention and would continue to be prosecuted.

Claim Rejections under 35 U.S.C. § 103

Claims 1, 6-8, 10, 27, 29, and 30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gillies *et al.* (1993, *Bioconjugate Chem.* 4:230-235, hereinafter "Gillies") in view of Gray *et al.* (U.S. Patent No. 6,444,792, hereinafter "Gray"), as evidenced by Ravetch (1997, *Current Opinion in Immunology*, 9:121-125, hereinafter "Ravetch"). Applicants respectfully traverse the rejection as applied to the pending claims.

Claim 1 and those depending therefrom (6-8, 10, 29, and 30) are directed to a region of a gene construct encoding an antibody-based fusion protein including, at its 5' end, nucleotides

encoding at least a portion of an IgG1 CH2 domain, with a mutation or a deletion reducing binding affinity for an Fc receptor, and at the 3' end, nucleotides encoding a non-Ig protein.

As acknowledged by the Office action, while Gillies teaches a fusion protein in the appropriate orientation *i.e.* Ig-IL-2, Gillies does not teach mutations that would increase the serum half-life of the Ig-IL-2 fusion protein. However, the September 30, 2004, Office action suggests there is a motivation to combine Gillies with Gray to produce the applicant's claimed invention because Gillies allegedly wished to improve the serum half-life of Ig-IL-2, and Gray allegedly teaches modifications to fusion proteins that increase serum half life by modifying Fc receptor binding. However, Applicants respectfully submit, that Gray does not in fact teach that the mutations of his invention result in an immunoglobulin fusion protein with an improved serum half life. Consequently, Applicants submit that the deficiencies of Gillies cannot be remedied by the addition of Gray.

Firstly, while the September 30, 2004, Office action points out that Gray teaches "the CH2 domain may be modified to reduce interactions with Fc receptors" and that "such modifications are useful for decreasing complement activation and phagocytosis (Col. 9, lines 60-64; Col. 4, lines 24-33)," nothing in Gray teaches or suggests that these modifications result in immunoglobulin fusion proteins with longer serum half-lives. In fact, Gray states only that the CTLA4-immunoglobulin fusion proteins according to his invention, which may be mutated to reduce effector functions, "display a <u>long</u> plasma half-life *in vivo* (Col. 9, lines 33-35)," not a <u>longer</u> half-life than fusion proteins without the mutations. Given that protein constructs containing an Fc portion were known by those skilled in the art to have already long serum half-lives, it is not surprising that Gray's mutated CTLA4-Ig fusion protein, which contains an Fc portion, has a long serum half-life. There is no indication that Gray appreciated or taught that mutations to the Fc region can result in <u>lengthened or improved</u> serum half-lives.

Further evidence that Gray does not teach immunoglobulin fusion proteins with mutations that <u>lengthen or improve</u> serum half-life is shown by the data from his pharmacokinetic studies. In his analysis, Gray compares the serum half-life of wild type CTLA4-IgG1 and a version of CTLA4-IgG4 mutated to contain nucleotide changes in the CH2 domain to replace amino acids thought to be required for IgG binding to Fc receptors, and

complement activation (see Gray, col. 30, lines 21-29; and col., 40, lines 9-39). Despite the fact that wild-type IgG1 is known in the art to have high levels of Fc receptor binding, and that IgG4 is known in the art to have reduced levels of Fc receptor binding, which would be further reduced by the mutations of Gray, Gray concluded that "both CTLA4IgG1 and [mutated] CTLA4IgG4 have **similar clearance rates**...indicating a serum half life of approximately 4 hours" (col. 40, lines 35-39). Thus, Gray concluded that there was **no difference in the serum half-lives** of the two fusion proteins, despite the IgG1 and IgG4 fusion proteins having differing affinities for Fc binding, as known in the art. In other words, Gray found that the mutations to the CH2 domain that reduced Fc receptor binding did **not increase the serum half-life** of the modified Ig fusion protein. Moreover, a closer look at Gray's data showed that the β phase half-life of the wild type CTLA4-IgG1 was **longer** than the mutated CTLA4-IgG4, **not shorter.** In fact, the wild-type fusion protein had a β phase half-life of 288 minutes compared to 214.2 minutes for the mutant variety (see col. 40, lines 31 and 34). Consequently, Gray's data does not show that reducing Fc receptor binding increases the serum half-life of Gray's fusion protein. Therefore, Applicants respectfully submit that a person skilled in the art would not be motivated to modify the fusion protein of Gillies according to the teachings of Gray because Gray does not teach or appreciate that the serum half-life of the modified fusion protein would in fact increase.

Despite the arguments presented above, the Office action, dated June 21, 2005, further asserts that Gray teaches molecules with decreased Fc receptor interaction, and that by decreasing Fc receptor interactions, the serum half-life of the fusion protein would increase. The Office action suggests that whether Gray appreciated it or not, "Fc receptors are involved in determining the half-life of immunoglobulins, and consequently fusion proteins comprising immunoglobulins" (page 4, lines 14-16).

In support of this proposition, the Office action cites the teachings of Ravetch which states that Fc receptors are involved in the "determination of serum immunoglobulin half-life (page 121, 1st column). Ravetch further teaches that antibody binding to the FcRp (protection receptor) and FcRn (neonatal receptor) is postulated to be related to antibody-half life (page 122, 2nd column). However, Applicants submit that the Fc receptor "FcRn" and "FcRp" as taught by

Ravetch are not the same as the Fc receptors (FcR, *e.g.*, FcγRI, FcγRII, and Fc γRIII) claimed by the applicant.

Fc receptors (FcR, *e.g.*, FcγRI, FcγRII, and Fc γRIII) as claimed by the Applicant refer to extracellular receptors for IgG-type Fc domains, involved in the recognition of objects coated with antibodies. Binding to an FcR receptor involves amino acids around residues 234-237 and also the N-linked oligosaccharide at Asn 297. This recognition occurs at a single site around the hinge region and is therefore not the same as the region for FcRn/FcRp recognition.

On the other hand, the primary purpose of the FcRn and FcRp receptor is to recycle antibodies out of cells after they have been internalized. Binding to the FcRn or FcRp receptor involves amino acids around histidine 435 of the immunoglobulin, around the CH2-CH3 junction region. It is well known in the art that mutation of this site has the effect of reducing, rather than increasing, serum half-life of antibodies. Applicants submit that this observation has lead to statements in the scientific literature to the effect that "Fc receptors can affect serum half-life of antibodies," such as those made by Ravetch, but that this refers specifically to the FcRn or FcRp receptor. No where does Ravetch teach or suggest that an antibody's affinity for FcR receptors, as claimed by the Applicants, has any relation to the antibody's serum half-life.

Consequently, Applicants submit that, in contrast to the Office action's position, Gray could not have appreciated that fusion proteins comprising modified CH2 domains would result in increased serum-half life as a result of reduced FcR receptor binding affinity.

For the reasons outlined above, Applicants respectfully request that the rejection of claim 1, and dependent claims 6-8, 10, and 29-30 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Claim 1 is also rejected under 35 U.S.C. § 103(a) as being unpatentable over Gillies *et al.* (1993, *Bioconjugate Chem.* 4:230-235, hereinafter "Gillies") and Gray *et al.* (U.S. Patent No. 6,444,792, hereinafter "Gray"), in view of Winter *et al.* (U.S. Patent No. 5,624,821). Applicants respectfully traverse the rejection as applied to the pending claims.

Applicants submit that neither Gray nor Winter provides a motivation to modify the construct of Gillies to incorporate a mutation at position 234, 235, 236, 237, or 297. The Office

action of September 30, 2004, alleged that Gray provided such a motivation by teaching "the benefits of engineering antibody-based fusion proteins with reduced affinity for Fc receptors (Office action, p. 7). Gray, however, does not teach that reducing affinity for Fc receptors is associated with an increased serum-half life, as discussed in detail above, and provides no (other) motivation for reducing the affinity of the constructs of Gillies for Fc receptors. Winter similarly fails to provide such a motivation. Absent such a motivation, the cited references cannot render the claim invention obvious. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claim 1 under 35 U.S.C. § 103(a).

Claim 4 is directed to an antibody-based fusion protein comprising at least a portion of a CH2 domain, wherein said CH2 domain is an IgG3 CH2 domain comprising a mutation or deletion that reduces binding affinity for an FcR receptor, and the antibody-based fusion protein has a longer circulating half-life *in vivo*.

Claim 4 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Gillies *et al.* (1993, *Bioconjugate Chem.* 4:230-235, hereinafter "Gillies") and Gray *et al.* (U.S. Patent No. 6,444,792, hereinafter "Gray"), in view of Michaelson *et al.* (U.S. Patent No. 5,348,876). Applicants respectfully traverse the rejection as applied to the pending claims.

The Office action suggests that one skilled in the art would be motivated to combine the teachings of Gillies, Gray and Michaelson to arrive at Applicants' claimed invention. Firstly, the Office action suggests that Gillies teaches IL-2 antibody-based fusion proteins have a high clearance rate, and Gray teaches that mutations in an IgG3 domain can result in reduced effector functions, *i.e.* Fc receptor binding. (Office action, June 21, 2005, page 6). The Office action further states that because of sequence similarity between IgG1 and IgG3, one of skill in the art would be motivated to incorporate the IgG3 mutations of Michaelson into the construct of Gillies.

Applicants respectfully submit, however, that Gray does not in fact teach that the mutations of his invention result in an immunoglobulin fusion protein with an improved serum half life, as discussed above. Consequently, Applicants submit that the deficiencies of Gillies cannot be remedied by the addition of Gray.

Applicants further submit that neither Gray nor Michaelson provides a motivation to modify the construct of Gillies to incorporate a mutation at position 281, 282, 283, 344, 378. As previously stated, Gray does not teach that reducing affinity for Fc receptors is associated with an increased serum-half life, as discussed in detail above. Further, Gray provides no (other) motivation for reducing the affinity of the constructs of Gillies for Fc receptors. Michaelson similarly fails to provide such a motivation. In fact, Michaelson does not even teach Fc receptor binding. Absent such a motivation, the cited references cannot render the claim invention obvious. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claim 4 under 35 U.S.C. § 103(a).

Claim 27 is directed to an antibody-based fusion protein comprising a variable domain and a portion of an IgG4 CH2 domain, the C-terminus of which is linked to the N-terminus of a non-Ig protein, wherein said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein. As discussed above, the Office action claims that there is a motivation to combine Gillies and Gray to create the applicants claimed invention because Gray allegedly teaches modifications to fusion proteins that increase serum half-life, and Gillies allegedly was trying to improve the serum-half life of Ig-IL-2 in order to improve targeting of IL-2 to tumor cells. However, Applicants respectfully submit that there is no motivation to combine Gillies and Gray to produce the applicants' claimed invention because Gray does not, in fact, teach that an antibody-based fusion protein comprising an IgG4 CH2 domain would have a longer circulating half-life than an IgG1-containing fusion protein. Applicants incorporate herein the arguments made *supra*, in relation to the rejection of claim 1 under 35 U.S.C. § 103(a). For these reasons, Applicants respectfully request that the rejection of claim 27 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that the pending claims presented for consideration herein are in condition for allowance. If the Examiner would like to discuss any outstanding issues, she is invited to telephone the undersigned.

Respectfully submitted,

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